

Bioequivalence of Biotherapeutics - Looking Beyond Bioavailability and Pharmacodynamics

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Introduction

Demonstration of bioequivalence among biotherapeutics poses unique and much more serious challenges than those arising from differences in the chemical composition of different biotherapeutics—namely variable immunogenicity and variable anaphylaxis. These problems may indeed arise not from the biotherapeutic proteins, but rather from excipients in the final formulations. For example variable oxidative damage is caused by reactive hydro- and alkyl-peroxides, epoxy acids, and aldehydes, which spontaneously arise in all lots of polysorbate 80 (Tween 80) and polysorbate 20 (Tween 20), along with varying amounts of unreacted starting materials, all of which are found in differing amounts (more than by an order of magnitude in the case of peroxides) from lot-to-lot and from different manufacturers. Perhaps most significantly, there is also now a growing awareness that polysorbates are intrinsically anaphylactogenic [1].

As a further complication, differences in the immunogenicity and anaphylaxis profiles of biotherapeutics may only become apparent once the product has been administered over an extended period of time to a sufficiently large number of patients. So while two biotherapeutics may superficially appear to be similar, differences in the protein API (e.g., amino acid sequence or glycosylation) and formulation components, particularly the polysorbates which are present in roughly 70% of all biotherapeutics, mean that they are not likely truly bioequivalent in the same sense as small molecule drugs.

The addition of excipients, specifically surfactants, to ameliorate undesirable properties such as aggregation or short shelf life, or allow for increased concentration permitting smaller administration volumes, place the final products in a condition better suited for administration to patients. Since no biotherapeutic formulation can be perfect in all respects, the known limitations, deficiencies and risks associated with commercial biotherapeutic products must be balanced against the remarkable life-saving benefits which they afford with the aim of achieving an acceptable FDA or EMA regulatory compromise with respect to product safety.

The dramatic life-changing and life-saving increase in the use of monoclonal Antibodies (mAbs) in the treatment of neoplastic, autoimmune, and inflammatory diseases is an exciting development, but at the same time has led to a significant increase in hypersensitivity reactions, complicating their use as first-line therapies and limiting patient survival and quality of life. For example, hypersensitivity and anaphylaxis have been reported for adalimumab, abciximab, bevacizumab, brentuximab, certolizumab, cetuximab, etanercept, golimumab, infliximab, obinutuzumab, ofatumumab, omalizumab, rituximab, tocilizumab, and trastuzumab, all of which contain a polysorbate surfactant [1].

While regulatory agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) pay serious attention to, and growing concern about, immunogenicity and anaphylaxis, the root causes of anaphylaxis have received limited attention. Anaphylaxis is often attributed to some undefined, unavoidable, intrinsic property of the biotherapeutic protein, essentially ignoring the potential contributions to anaphylaxis by polysorbates (PS-20 or PS-80 – Tween-20 and Tween-80, respectively) which are actually incorporated in approximately 70% of all mAb formulations.

As aggregation preventers polysorbates are highly effective. However, the contaminating immunogenic (neoantigen-forming) and anaphylactogenic (anaphylaxis-stimulating) chemical species – the hydro- and alkyl-peroxides, epoxy acids and reactive aldehydes such as formaldehyde and acetaldehyde – cannot be avoided. Even following chemical purification, peroxides are detectable within two weeks after first exposure to air.

It has now been demonstrated in well-documented human patient anecdotal reports and extensively in animal model studies employing a broad spectrum of functionally independent indicators such as histamine release, hemodynamic effects, skin prick testing, enzyme-linked immune sorbent assay, IgE immunoblotting, flow cytometric detection of basophil activation, complement activation, determination of certain humoral factors, and the absence of polysorbate specific IgE, that polysorbates are intrinsically anaphylactogenic [1].

Both unwanted immunogenicity and anaphylaxis comprise major components of safety assessment. Replacement of anaphylactogenic and immunogenic functional excipients with equally effective but safer alternatives will allow biotherapeutic developers to differentiate their biotherapeutic, biosimilar, or biobetter product from the large number of nearly identical competitor products, simultaneously providing an unmatched

commercial benefit as well as critical clinical benefits for all concerned – patients, physicians, and third party payers.

References

1. Maggio ET. Reducing or Eliminating Polysorbate Induced Anaphylaxis and Unwanted Immunogenicity in Biotherapeutics. *J Excipients and Food Chem.* 2017;8(3):52-61.